Division of Consumer Affairs

IN THE CHANCERY COURT FOR DAVIDSON COUNTY, TENNESSEE
FOR THE TWENTIETH JUDICIAL DISTRICT AT NASHVILLE

STATE OF TENNESSEE,
Petitioner,

v.

KNOLL PHARMACEUTICAL COMPANY,
a BASF Corporation

Respondent.

ASSURANCE OF VOLUNTARY COMPLIANCE AND DISCONTINUANCE

1.1 This Assurance of Voluntary Compliance and Discontinuance ("Assurance") is entered into by the Attorneys General of the States of Arkansas, Arizona, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Rhode Island, South Carolina, Tennessee, Texas, Vermont, Virginia, Washington, West Virginia and Wisconsin ("States"), acting pursuant to their respective consumer protection statutes, and Knoll Pharmaceutical Company, and BASF Corporation ("Respondents").

1.2 Knoll Pharmaceutical Company ("Knoll")") is a New Jersey corporation engaged in, among other things, the discovery, development, manufacture and sale of pharmaceutical drugs. Knoll's corporate headquarters are located at 3000 Continental Drive North, Mount Olive, New Jersey, 07828-1234. Knoll is a wholly owned subsidiary of BASF Corporation.

1.3 BASF Corporation ("BASF") is a Delaware corporation engaged in the business of, among other things, the manufacturing and selling of pharmaceutical drugs through its various subsidiaries, one of

which is Knoll. BASF's principal place of business is located in Mount Olive, New Jersey.

STATES' POSITION

2.0 The statements contained in this Section 2 represent the position of the States only and Respondents do not admit the truth of any of the statements contained in this Section.

2.1 Hypothyroidism is a medical condition in which a person's thyroid gland does not produce sufficient thyroid hormone. The common treatment for this condition is the prescription drug, levothyroxine sodium. Over eight million patients in the United States take levothyroxine sodium at any given time.

2.2 Synthroid®, manufactured and sold by Knoll, is the dominant and most expensive brand of levothyroxine sodium product on the market.

2.3 In 1987, Flint Laboratories ("Flint") was the manufacturer of Synthroid®. In or about May 1988, Flint signed a contract with Betty J. Dong, Pharm. D., at the University of California at San Francisco Medical School ("UCSF") to design and perform a research study ("Dong Study") assessing the bioequivalence of Synthroid® and three other levothyroxine sodium products.

2.4 By the end of 1990, Dr. Dong completed the study and sent study samples to Boots Pharmaceuticals, Inc. ("Boots"), which, in the meantime, had acquired Flint. In the opinion of the researchers who worked on the Dong Study, it demonstrated that all four levothyroxine sodium products were bioequivalent.

2.5 Over the next five years, Boots engaged in a campaign to discredit Dr. Dong's study and to prevent publication of the results. Boots claimed that the Dong study failed to analyze alleged changes in TSH levels. However, Boots itself had approved each element of the Dong study, including its focus on T4 rather than TSH. Moreover, expert consultants stated that the study showed bioequivalency of Synthroid and the other three products studied, that any possible flaws in the study were unimportant, and that they believed the study's conclusions that the four products were bioequivalent. In addition, two subsequent investigations by UCSF found no significant problems with Dr. Dong's study. UCSF found the study to have been conducted in a manner that complied fully with its contract with Boots.

2.6 In April 1994, Dr. Dong submitted the manuscript of her study to the Journal of the American Medical Association ("JAMA") for possible publication. JAMA sent the manuscript to five expert reviewers. The manuscript was revised incorporating their suggestions and was accepted for publication in JAMA in November, 1994. Boots denied Dr. Dong permission to publish the study, citing its contract. On or about January 13, 1995, Dr. Dong abruptly withdrew the manuscript from publication, giving her reason as "impending legal action by Boots Pharmaceuticals. Inc. against the University of California, San Francisco and the investigators."

2.7 In March, 1995, Boots' was merged into Knoll. Knoll assumed all obligations and liabilities from Boots' activities for selling and marketing Synthroid®. Knoll obtained the rights to produce and

manufacture Synthroid®.

2.8 While Respondents knew of the Dong study and its conclusion, they nonetheless continued to market Synthroid® as unique and superior to competing levothyroxine sodium products.

2.9 In fact, Respondents promoted Synthroid® through the use of an article ("Berg/ Mayor article") which misleadingly failed to disclose the existence of the Dong Study and its conclusions. Beginning in 1994, the FDA queried the company's promotional use of the Berg/ Mayor article to show bioinequivalency among various levothyroxine sodium products and eventually on November 7, 1996, FDA sent a letter to Knoll which informed them that promotional use of the Berg/Mayor article constituted the misbranding of Synthroid®.

2.10 In a subsequent letter dated August 1, 1997, FDA informed Knoll that advertisements representing that Synthroid® was a reference product or standard for levothyroxine sodium products or that Synthroid® was superior to other levothyroxine sodium products or that no levothyroxine sodium product was equivalent to or useful in place of Synthroid®, also misbranded Synthroid® because Knoll had not made data concerning such claims available for independent review by FDA.

2.11 In November, 1996, Respondents finally agreed not to block publication of Dr. Dong’s study any further.

2.12 Dr. Dong's manuscript was published in the April 1997 issue of JAMA: Betty J. Dong et al., "Bioequivalence of Generic Brand-name Levothyroxine Products in the Treatment of Hypothyroidism," together with a lengthy editorial describing the events that led up to the publication. 277 JAMA 1205-I3; 1238-43 (1997); JAMA published the manuscript, as set in type two years previously, with none of the content changed.

2.13 From 1990 on Boots, and subsequently Knoll, engaged in conduct which included the concealing of information from governmental decision makers regarding the Dong Study and its findings. The Respondents failed to disclose to the FDA and the States the existence of the Dong Study and its findings, the fact that the Dong Study contradicted the Berg/Mayor article or the fact that Dong, based upon her 1990 findings, had reversed an earlier opinion that levothyroxine sodium products were not bioequivalent. Respondents did not provide the FDA and the States with the protocol or the underlying data supporting the Dong Study. The States did not see the study until it was published in JAMA.

2.14 Throughout the period 1990-1995, Boots, and subsequently Knoll, continued to provide the FDA, the States and the medical community a variety of materials, both published and unpublished, relating to levothyroxine sodium product bioequivalence. In 1990, for example, Boots sent FDA an unpublished in-house "study" purporting to show Synthroid’s® potency more consistent than that of a competitor. Boots said it was providing the unpublished material because potency of levothyroxine was a "major problem" and it had received "new information" which was both credible and objective. Nevertheless, Boots never provided the FDA with the Dong protocol, the unpublished results or the manuscript of the report on the

Dong Study, as the FDA had requested.

2.15 Additionally, despite warnings from the FDA, Knoll and its predecessors distributed promotional material to pharmacists which questioned the safety, quality and effectiveness of competitors' products. The FDA notified Boots that the use of promotional material which made superiority claims, such as "accept no substitutes," would in the FDA's words "not be tolerated." Boots itself had previously been cited by the FDA for distributing subpotent product. Further, the FDA had warned Knoll that it could not advertise that Synthroid® was superior to other levothyroxine sodium products or that levothyroxine sodium products were not bioequivalent.

2.16 On August 14, 1997, responding to concerns over questions regarding their stability and potency, the FDA placed a Notice in the Federal Register declaring that "orally administered drug products containing levothyroxine sodium are new drugs." The FDA called for current manufacturers to submit New Drug Applications ("NDA") for the levothyroxine products.

2.17 The States' position is that Respondents' conduct as set forth above violates the States' laws set forth in footnote 1 hereof.

RESPONDENTS' POSITION

3.0 The statements contained in this Section 3 represent the position of the Respondents only and the States do not admit the truth of any of the statements contained in this Section.

3.1 Respondents' position is that they did not violate any state or federal laws with respect to the marketing of Synthroid®, communications with the FDA or any other state or federal agency or person and assert properly exercised their contractual right to deny publication of the Dong Study.

3.2 Synthroid® (levothyroxine sodium, USP) marketed by Knoll Pharmaceutical Company, is the leading thyroid replacement hormone, and has been marketed for over forty years. Because Synthroid® is the most widely prescribed levothyroxine sodium product, its competitors have long tried to encourage switching of patients to their products by arguing that their products are bioequivalent to and cheaper than Synthroid®. Even though various levothyroxine sodium products have been available to all patients, there is a long standing debate over bioequivalence among levothyroxine sodium products.

3.3 When two drugs are bioequivalent, they can be freely switched without health risks or the need for additional testing and retitrating. "Bioequivalence" means that the drugs are pharmaceutically equivalent products that have comparable extent and rate of absorption when given the same dose under the same conditions. Unlike most other drugs, levothyroxine products are "narrow therapeutic index" drugs. This means that even a small amount of over- or under-dosing can cause serious medical problems, including heart, brain, psychological and fertility problems. Also, thyroid stimulating hormone ("TSH") must be analyzed and considered in assessing the bioequivalence of levothyroxine drugs. Thus, the general bioequivalence standards applicable to most drugs does not apply to drugs like Synthroid®.

3.4 Beginning in the 1980s, over 20 studies have attempted to determine bioequivalency of different levothyroxine sodium products and the results of the studies vary greatly on whether levothyroxine sodium products are or are not bioequivalent.

3.5 A study co-authored by Betty Dong, a Pharm D at the University of California, San Francisco, expresses the opinion that one branded and two generic products tested at two different doses are bioequivalent to Synthroid®. However, carefully read, the study added no new scientific information to that already available to the medical community, any state or federal agency or formulary board or the consuming public at large regarding the long-standing debate over the interchangeability of levothyroxine sodium products.

3.6 The Dong Study simply was neither an adequate nor well controlled study nor did it conclusively establish that complete interchangeability exists for levothyroxine products. Among the reasons some experts believe the study was inadequate was its failure to conduct an analysis of TSH.

3.7 The Dong Study analyzes bioequivalency by comparing blood levels of T4, the "delivered drug," and found that the products tested were within 80-120% of each other. Her study was based on only twenty-four subjects. Dr. Dong failed to disclose that well over half the study subjects went "out of range" when switched. The study compared Synthroid® to one branded and two generic products at two dosage levels out of eleven. Prior to the eventual publication of the Dong Study in 1997, both generic products referenced in the study were withdrawn from the market at the request of the manufacturer because of stability and manufacturing problems.

3.8 The substantial flaws in Dong's methodology and protocol were such that Knoll's criticisms of her study and its desire to terminate the study began in 1989, almost one and a half years before the initial results of the study were even known. After the initial results were reached, a primary and significant concern was that Dong failed to evaluate or comment upon the fact that sixteen of her twenty-four subjects showed unexplained changes in levels of TSH upon switching from one drug to another. TSH was measured but not analyzed in her study for bioequivalence. However, when the TSH data from the Dong study was analyzed, it was evidence that the TSH levels for the individual patients varied widely after switching B thus indicating that the study did not demonstrate bioequivalence.

3.9 In addition, (a) Dr. Dong refused to acknowledge that leading endocrinologists and medical societies recommend careful testing and retitration of patients after switching; (b) Dr. Dong refused to disclose that two of the three comparative drugs she used were pulled before publication by their manufacturer due to stability problems; (c) the bioequivalence guidelines used by Dong are recognized as being inappropriate for use with any of the narrow therapeutic range drugs; (d) Dong refused to acknowledge the higher risks of switching in certain patient groups such as pediatric patients and patients with thyroid cancer or heart disease; (e) Dong failed to ensure that each patient in her study was euthyroid for the re-study period, fasted before blood was drawn and took the correct amount of meditation; (f) Dong speculated about great cost "savings" if physicians would massively abandon use of Synthroid®, but failed to acknowledge the significant offsetting costs of switching (e.g., increased medical visits for new

prescriptions, retesting and retitration and unrealistic estimates that 100% of all physicians would so act); (g) two years after the publication of the Dong Study and its wide dissemination by Knoll's competitors, not even a small percentage of physicians, pharmacists or State Formularies have reacted by changing their prescribing habits or changing their formularies.

3.10 Originally Dr. Dong herself was the one who delayed publication. Dr. Dong did not complete the study until 1991 and it was not until 1994 that Dr. Dong first presented a draft manuscript and indicated she intended to publish the study. Knoll repeatedly attempted to have the flaws corrected or at least addressed so that the paper could be published.

3.11 Indeed, Knoll had offered to allow publication so long as the Dong Study referred to contents of the professional guidelines for treating thyroid disease. Those guidelines, promulgated by the American Association of Clinical Endocrinologists ("AACE") and the American Thyroid Association ("ATA"), state that, in order to protect the patient's health and well being, retesting and retitrating is recommended when switching levothyroxine products.

3.12 Knoll executives believed that publication in this form was unacceptable because it posed health risks to thyroid patients and thus initially refused permission to publish in the 1995 time frame. Initially the university had refused to support her when Knoll denied permission to publish because Dr. Dong had contracted with Knoll to allow control over publication.

3.13 Ultimately, in late 1996, Knoll and the University of California reached agreement on the publication of the paper accompanied by Knoll's objections, which occurred in April 1997.

3.14 Synthroid® has been marketed for over 40 years and it is generally recognized as safe and effective. No levothyroxine sodium product is currently listed in the FDA Orange Book and no levothyroxine sodium product has been rated by the FDA as bioequivalent or bioinequivalent to any other levothyroxine sodium product.

3.15 The FDA has issued a Federal Register notice in which it announced its tentative determination that all levothyroxine sodium products are new drugs. It also recognized, however, that its tentative determination would require revision if one or more levothyroxine sodium products were not new drugs because they are generally recognized as safe and effective or otherwise exempt from the requirement of a New Drug Application ("NDA"). Accordingly, the FDA invited submission of Citizen Petitions seeking a determination of whether a product is generally recognized as safe and effective and Knoll has submitted such a petition for Synthroid®.

3.16 The FDA has twice informed one of Synthroid’s® competitors that its advertisements were "misleading." In a 1997 letter, the FDA emphasized that "levothyroxine products are not currently recognized by the FDA as bioequivalent." Likewise, in February, 1999, the FDA stated that "neither product has been demonstrated to be either equivalent to the other or inequivalent to the other. Thus, any claims of equivalence are unsupported." The levothyroxine sodium product that was the subject of these

letters was one of the products in the Dong study.

3.17 Currently, (a) Levothyroxine sodium products are not listed as bioequivalent in the FDA Orange Book; (b) the FDA has not determined whether or not levothyroxine sodium products are bioequivalent or bioinequivalent; (c) the FDA has recognized that levothyroxine sodium products are narrow therapeutic range drugs; (d) the FDA has admonished both Knoll and a Knoll competitor with respect to certain advertisements that suggest that Synthroid® and other levothyroxine sodium products are bioequivalent or bioinequivalent; and (e) the FDA position on the bioequivalence or bioinequivalence of levothyroxine sodium products remains unchanged.

GENERAL PROVISIONS

4.1 This Assurance does not constitute an admission by Respondents for any purpose, of any fact or of a violation of any state or federal law, rule or regulation. Respondents enter into this Assurance without admitting any wrongdoing and for settlement purposes only. This Assurance is made without trial or adjudication of any issue of fact or law. This Assurance does not constitute evidence or admission of any issues of fact or law. Respondents enter into this Assurance for the purpose of arriving at a complete, full settlement of any disagreement, as to the matters addressed in this Assurance and preceding its execution, which may exist between Respondents and the States, thereby avoiding unnecessary delay and expense.

4.2 This Assurance shall be governed by the laws of the above named States.

4.3 This Assurance does not constitute an approval by the States of any of Respondents' programs or practices and no Respondent shall make any representation to the contrary.

4.4 Nothing in this Assurance shall be construed as a waiver of any private rights of any person. Nothing in this Assurance shall permit any person or entity not a signatory hereto to enforce any provision of this Assurance.

4.5 Nothing in this Assurance shall be construed to authorize or require any action by Respondents in violation of applicable federal, state or other laws. Without restricting the manner in which such communication can be used, communications in the form of a letter to Respondents from FDA, including DDMAC, do not, in and of themselves, prove a per se violation of this Assurance. Respondents agree that this Assurance constitutes a legally enforceable obligation of Respondents in accordance with its terms.

4.6 This Assurance may be executed in counterparts.

4.7 The signatory States shall not institute any civil proceeding or take any civil action against Respondents under the States' above cited consumer protection statutes for any conduct prior to the date this Assurance is signed, based on any program or practice which is addressed in this Assurance.

4.8 The respective Attorneys General of the States, without further notice, may make ex parte application to any appropriate state court for an order approving this Assurance, which shall be considered an Assurance of Voluntary Compliance or an Assurance of Discontinuance as provided by the States' respective laws, or otherwise file this Assurance in any appropriate state court.

4.9 This Assurance applies to Respondents, together with their subsidiaries, employees, successors, and assigns of each and to agents of Respondents who are engaged in promoting levothyroxine sodium products, writing, producing, developing or delivering any program, plan, material, script advertisement or any other promotional activity, including without limitation, any physician, researcher or other professional whether compensated directly or indirectly, by cash payment or by any other means.

4.10 Respondents shall institute supervisory compliance procedures which are reasonably designed to insure compliance with this Assurance, including, without limitations, the training of relevant employees, revisions to and/or development of appropriate training materials and the development and implementation of internal procedures, including periodic monitoring to ensure compliance with the terms of this Assurance.

ASSURANCES

5.1 Respondents shall not make any false, misleading or deceptive claim regarding Synthroid® or any other levothyroxine sodium product (hereinafter both referred to as "Product") in advertising, promotion or labeling, including, but not limited to, any false, misleading or deceptive claim regarding:

(a) the quality of manufacture or performance of the Product;

(b) the reliability or consistency of the Product;

(c) the safety or effectiveness of the Product;

(d) superiority or other characteristics of the Product;

(e) bioequivalence of the Product to any other drug or new drug, or lack thereof;

(f) the status of the Product as a reference, standard or "medically necessary";

(g) the safety or cost of switching the Product;

(h) any other manufacturer's Product;

(i) any medical rationale for specifying the use or continued use of one Product over another;

(j) benefits and risks of using the Product;

(k) the scope, findings or existence of any scientific study, whether published or not, concerning the Product.

RESOLUTION

6.1 Respondents shall provide a copy of this Assurance to all those officers and employees of Respondents who may have managerial responsibility for developing, conducting or authorizing programs involving promotion of levothyroxine sodium products, and to all employees who are involved in the promotion of levothyroxine sodium products to third parties and to any other individual or entity through whom Respondents may act, who or which may have managerial responsibility for developing, conducting or authorizing programs involving promotion of levothyroxine sodium products.

6.2 No later than (90) ninety days following the execution of this Assurance, Knoll shall provide to each of the States a report setting forth in detail all steps Knoll has taken to comply with the terms of this Assurance.

6.3 This Assurance constitutes the entire agreement of the parties hereto and supersedes all prior agreements or understandings, whether written or oral, between the parties and/or their respective counsel with respect to the subject matter hereof. Any amendment or modification to this Assurance must be in writing and signed by duly authorized representatives of all the parties hereto.

6.4 Respondents agree to pay, within thirty (30) business days after the execution date of this Assurance, the sum of forty one million eight hundred thousand dollars ($41,800,000.00) to the States, in individual checks made payable to such accounts and addresses as the Attorneys General shall direct. Such sum is to be divided by the States as they may agree and is to be used by the individual States for attorney’s fees and investigative costs, and may be designated for those purposes or for consumer education, litigation, public protection or local consumer aid funds or any other purpose authorized by state law at the discretion of each state’s Attorney General.